Real Time Monitoring in the Control Theory Paradigm

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Monitoring patients hospitalized in hemato-oncology departments to undergo clinical protocols of therapy is a complex task. The main difficulty arises in the follow-up of the oncology protocol and in the management of critical episodes of acute illness which frequently occur due to the high toxicity of the antimitotics used. This problem can be conceptualized within the control theory paradigm as the task of controlling a process whose state can deviate unacceptably from a normal range. Following the control theory analogy at the level of knowledge bases design, we have modeled the medical knowledge as control information to represent the medical actions, and state information is used as a feedback control to readjust the command.

INTRODUCTION

Following up patients hospitalized in hemato-oncology departments to undergo chemotherapeutic protocols is a complicated task. One reason is that oncology protocols are very sophisticated treatment plans made of associations of highly toxic antimitotics. The other reason is that adverse effects often occur that require under time pressure difficult diagnosis and treatment.

On the request of a French clinical department of hemato-oncology, we have developed an intelligent patient monitor, named SEPIA [1, 2], to assist clinicians in adhering to well-defined oncology protocols as well as in the management of critical episodes of acute illness. Close to Guardian [3], SEPIA is able to control the monitored data, summarize the patient's condition, alert clinicians to imminent aggravations, recommend appropriate laboratory tests to diagnose newly appeared pathologies, and propose a suitable therapy plan.

Classical knowledge-based systems usually solve static problems, i.e., problems that are stated at the beginning of the reasoning process and which do not evolve as the process progresses. But monitoring patients subjected to aggressive chemotherapeutic protocols is quite different. The observed results of the inferences recommended by the system must be continuously integrated to readjust the context in which the changing clinical patient condition needs to be interpreted. Therefore, a feedback loop has to be introduced to control the process. Considering the patient as a physiological dynamic system, we have followed the metaphor with control theory at the level of the knowledge base design. The medical knowledge has been modeled as a control information to represent medical actions, and a state information to manage patient monitoring.

PATIENT MONITORING IN SEPIA

Control theory is used when a dynamic process which can deviate from a planned program has to be controlled, or commanded. The control information defines the program of the conducted process. The state information consists of a description at any time of the state of the process. The management of these two types of information aims at permanently readjusting the control on the basis of the state information, to generate the orders that would be communicated to the operators, so that the process behaves as expected. The information management module is generally based on a mathematical model of the process.

Control theory actors such as state information, control information and information management are represented in SEPIA whose global functioning is illustrated by the block diagram on Figure 1. In the same way, monitored data are continuously abstracted into state values which activate the factual knowledge bases through the PSM updating module. This generates appropriate medical prescriptions which are integrated to the currently processed oncology protocol. As a result, the Patient Specific Model (PSM) is updated to restore the control information in a patient specific care plan, which is then operationalized by the command operationalization into executable prescriptions for the nurse team.

SEPIA's Controller

Processing the information coming from several sources of knowledge to dynamically produce the current executable nursing care plan, SEPIA's controller plays the role of the information management entity. SEPIA's controller is constituted

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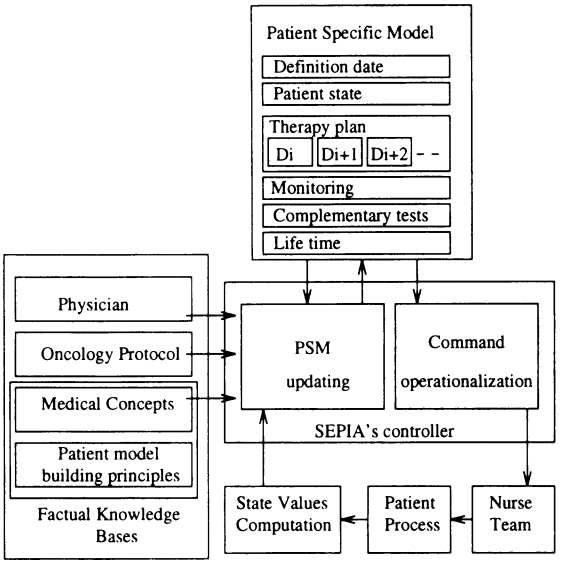

Figure 1: SEPIA's control of the patient process.

of two different modules, one is in charge of the PSM updating, and the other has to operationalize the patient specific treatment plan into an executable nursing care plan.

The PSM updating module has to interface with the different sources of information: the state values, the medical concepts and patient model building principles, i.e., the factual knowledge bases, the oncology protocol, and the physician. State values lead the PSM updating module to activate the factual knowledge bases which generate diagnostic, monitoring, and therapeutic prescriptions. These prescriptions are integrated to the part of the oncology protocol which is currently operating to readjust the running PSM. As an open-loop control system, SEPIA's recommendations should be acknowledged before being implemented. So, the physician validates the proposed PSM, and the resulting acknowledged PSM is then operationalized by the command operationalization module, which produces a plan of executable commands to be carried out by the nurse team.

Patient Specific Model

In hemato-oncology, classical pathophysiological schemes are deeply perturbed by the chemotherapeutic course. Future patient states prediction, based on an explicitly stated model, is not possible. However, rather than attempting to foresee all possible evolutions, one aims to provide an optimal monitoring in order to rapidly detect complications and avoid irreversible states, in parallel with conducting the oncology protocol. The PSM used in SEPIA is therefore quite different from the mathematical model operating within control theory, though similar in role. It is also different from its symbolic equivalent which would have been a qualitative model. SEPIA's PSM is defined by patient specific information. This includes past and current patient states summarized by the state values, the patient specific care plan, the definition date t of the PSM and its life time or "persistence" defined as the maximal frequency with which the model must be updated. The model structure is characterized by the nature of patient specific medical actions; the quantitative characteristics of these medical actions, mainly temporal, are the model parameters. As a result, no prediction of future patient states can be provided by the instantiation of a state equation as in the original control theory, or by running a pathophysiological model as would be the case in a qualitative version of the control theory methodology. On the contrary, model parameters behave as random variables that should be continuously estimated. The model structure could also change unexpectedly and should be accordingly updated. When no new monitoring data are processed, the default frequency of the plan adjustment is given by the PSM life time.

Factual Knowledge Bases, and Physician

The patient specific care plan is made of medical prescriptions which correspond to the control information. These prescriptions may either come from the physician, the oncology protocol, or the factual medical knowledge bases.

The oncology protocol is the standardized treatment plan imposed on cancer patients. It is represented as conditional sequences of prescriptions which are triggered when the protocol is activated. The declared knowledge includes the modalities of the different drug administrations (form, route, dose, frequency, duration, ...), and determines the "strategic level" [4]. Protocol-derived prescriptions also include the instructions for a basic follow-up of patients. This minimum monitoring aims to manage the classic disturbance which results from the toxic effects of the used drugs. However, beyond the forecast complications of the patient state, usually monitored by oncology protocols, unexpected deviations, evaluated by state variables, often occur and may lead to severe patient injury. From the state information, the factual knowledge bases are activated and generate the appropriate prescriptions to diagnose, monitor and treat these serious adverse effects. As a consequence, complementary short-term therapy plans or subprotocols, the "adjusted level" [4], have to be dynamically integrated in the oncology protocol. This leads to a more complex definition and management of patient specific treatment plans.

STATE INFORMATION

General Presentation

Coupled with the oncology chemotherapy, the patient viewed as a process is not well understood. Changes in the patient's state are rather unpredictable. Following control theory, state variables have been introduced to assess the patient state in order to evaluate how he or she reacts in response to the control information represented by the oncology protocol. The process is driven by discrepancies between what things ought to be and what they actually are. How things ought to be is evaluated by the PSM and how things actually are is measured by state variables. State values generate the feedback which allows the system to readjust the control of the patient process by both model structure and model parameters updating.

As opposed to factual knowledge which corresponds to medical concepts and patient model building principles, state variables represent the reasoning knowledge [3]. This reasoning knowledge is formalized as discrete reasoning operations triggered by the monitored data. As in the control theory paradigm, we have defined nine knowledge units or state variables to represent the major human physiological devices, and therefore almost entirely characterize the dynamic behavior of the patient condition. These nine state variables are the renal, hepatic, hematologic, cardiac, pulmonary, intestinal, neurologic, dermatologic, and infectious states.

Data Reduction

Oncology recipients are critically ill patients, for which numerous data are collected through frequent observations and testing in addition to continuously monitoring equipment. To efficiently handle the information, a major phase in the system reasoning process is to reduce the enormous amount of the monitored data [3, 5] to nine state values. Different abstraction levels have been introduced as suggested by Miller in [6]. Patient history hints, clinical auscultation findings, and complementary laboratory tests, constitute the set of elementary data, also called *parameters*, which describe at the lower level of abstraction, a patient's condition. However, this representation based on an unstructured collection of data does not permit to reason or take decisions since the tremendous amount of parameters obstructs a clear focus on the critical information. Therefore, interpreted values have been associated to each parameter. They correspond to the "qualitative values" of [7] and are called *synthesis values*. Synthesis values are dynamically defined within the parameter to which they are related. For instance, if the uremia count is 17 mM/l, the corresponding synthesis value hyperuremia is computed as soon as the parameter value is entered into the system. This first level of abstraction allows to discriminate easily between normal values and abnormal values and facilitates the elaboration of reasoning strategies used in the state value evaluation. But, this first level of abstraction does not summarize the information about a patient condition, since the number of computed synthesis values is as great as the original number of parameters from which the synthesis values have been generated. To summarize patient information we have gathered data in *syndromes* which are both medically significant and pertinent for the reasoning process. The ultimate level of the abstraction hierarchy is the *state value*, which represents the most synthesized view of all the monitored data.

State Variables Representation

For each state, the medical expertise is described by a set of heuristics structuring a generality ordered tree of state values. The depth levels indexed by the request or the results of appropriate complementary tests whose knowledge permits diagnostic refinement, correspond to the progressive steps of both diagnostic and therapeutic processes. Each level is determined by etiologic guidance, and associated, in factual knowledge bases, to diagnostic actions, therapeutic recommendations and monitoring prescriptions that take into account the efficiency of the planned treatment while controlling the patient condition evolution.

Tree of Sub-states: Some state variables are represented as AND-TREEs whose nodes are sub-states. This is the case of a state variable combining independent processes that may be simultaneously affected. For instance, the hematologic state is made of the hematopoietic sub-state, the hemostatic sub-state and the blood peripheral precursors sub-state. Another case is that of a state variable which corresponds to a unique physiological entity, but whose components play different physiological roles. For instance, in the cardiac state, the right and left sides have different functions and may therefore develop different pathologies.

Tree of Values: When different diseases concerning a given state variable cannot co-occur, for instance because they correspond to antagonist processes, the state is simply represented by an OR-TREE of exclusive values. Each state variable is defined by a set of evaluation constraints which are the particular medical data which, as soon as they are entered into the system, activate the evaluation of the state variable. The state evaluation is a top-down process. Conducted from the root, this process is driven by state-specific criteria which allows, when the information is avail-

able, the system to refine the state values up to the diagnosis.

The first step of the evaluation process concerns the distinction between normal and abnormal values and is based on state-specific indicators which are regularly monitored, e.g., the temperature for the infectious state, the hemoglobinemia for the red-cell line state, etc. When state values are not normal, for instance, when the chest radiography is pathological for the pulmonary state, the state value evaluation process is carried on. At each level, the process is indexed by the data which are needed to discriminate between the different possible paths. Two cases can be encountered: i) all the data are available to the system either because they belong to the routine monitoring of the state which is currently processed or because they are involved in the evaluation of some other state which is pathologic and requires a sustained monitoring. The evaluation may thus go on until the diagnosis or the etiology; ii) some data necessary to discriminate between a few intermediate state values are not available at the moment of the evaluation process. In this case, the evaluation stops before the state value is completely specified. On the basis of partial state values, the factual knowledge bases are activated: the complementary tests needed to get the missing information are identified and requested, the monitoring prescriptions are refined (increased when there is an alteration of the patient condition, relaxed when there is an improvement in the patient condition). A symptomatic treatment, readjusted when the etiology is finally known, may also be suggested.

EXAMPLE

A simulated running session is presented in order to illustrate how SEPIA monitors patients subjected to chemotherapy protocols. We consider the case of a 65-year-old man, admitted to the hemato-oncology department because of persistent low-grade fever, fatigue, deterioration of general condition, and weight loss of 4-5 kgs for approximately one month.

Table 1: Laboratory results.

	D-0	D-8
Hemoglobinemia (mg/dl)	11	8
White-cell count (per mm^3)	22000	1000
Platelets (per mm^3)	85000	45000
Calcemia (μMol/l)	4.5	-

On arrival, denoted D-0, the temperature is 38°C and the physical examination discloses lymph nodes and splenomegaly. Laboratory studies are performed (Table 1), a lymph node punction and a bone marrow smear reveal an infiltration of large cells. The final diagnosis of leukemic non Hodgkin's lymphoma is made, and a four-day long chemotherapeutic course made of Cyclophosphamide, Hydroxo-doxorubicine, Oncovin and Prednisolone, or CHOP, is applied. The PSM is initialized as illustrated in Figure 2.

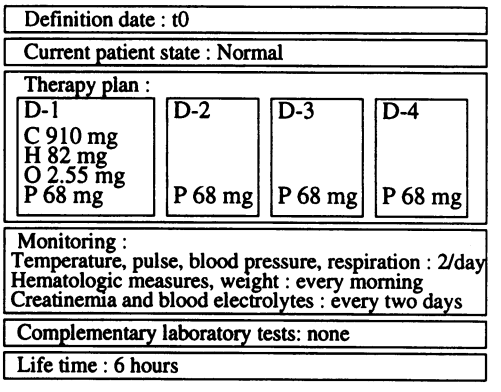

Figure 2: Initial PSM.

On day 4 (D-4), the patient has no more fever, the calcemia is normal, which indicates that the disease has been controlled. During the four days, all monitored data are normal leading SEPIA to compute normal state values, and keep the originally planned PSM. But on D-8, the patient complains about a right thoracic pain. The temperature is 37°C, the pulse is 140, and the respiration is 35. The blood pressure is 90/60 mmHg, hematologic values are deeply disturbed (Table 1). These data trigger the evaluation of state values. The observed dyspnea, as an evaluation constraint of the pulmonary state, activates the evaluation of the pulmonary state. In the same way, hemoglobinemia activates the evaluation of the red-cell line state, the white-cell count activates the evaluation of the white-cell line state, and the platelet count activates the platelet line state.

To simplify the presentation, we just consider the pulmonary state (see Figure 3). The chest radiography being unknown, no pulmonary value can be set. However the factual knowledge bases are activated and a chest radiography is prescribed to progress in the pulmonary state evaluation, as well as blood gases in order to evaluate the respiratory function. The hematologic state is abnormal with the development of an aplasia (anemia + neutropenia + thrombocytopenia) resulting from the CHOP course. The new prescriptions are integrated by SEPIA's controller to update the PSM. The complementary exams are performed and 30 mn later, blood gases results are available disclosing a PO2=45mmHg, a PCO2=38mmHg, and a

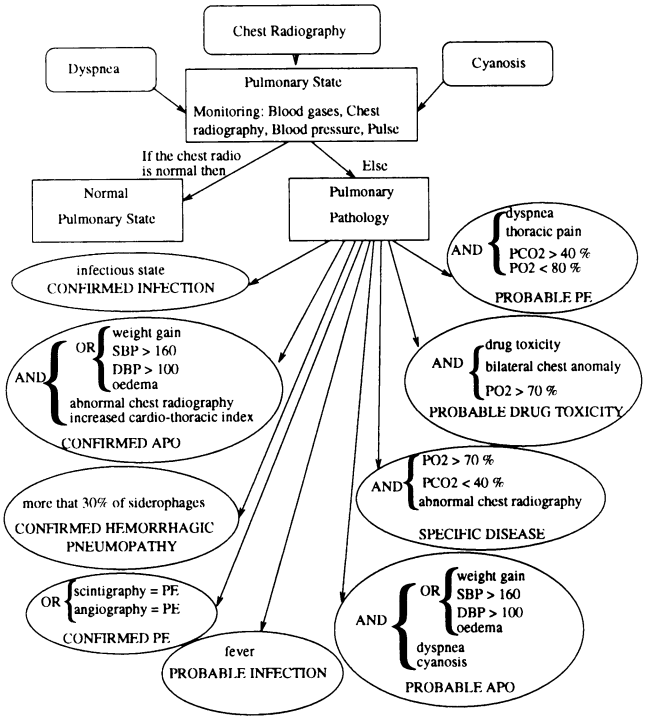

Figure 3: Pulmonary state representation.

PH=7.36. These new data activate the state values computation process, but since there is no modification of the previous state values (the chest radiography is still unknown), the PSM updating amounts to simply deleting the blood gases from the complementary laboratory exams to do. One hour later, the chest radiography is done revealing a right paracardiac opacity. This new information allows the system to discriminate between normal pulmonary state and pulmonary pathology. Then, since there is neither infection, nor any proof of Acute Pulmonary Oedema (APO), nor any evidence of hemorrhagic pneumopathy, nor scintigraphy or angiography to establish a confirmed Pulmonary Embolism (PE), nor fever, nor clinical sign of APO, nor specific disease, nor drug toxicity, SEPIA suggests it could be a PE, and asks for a scintigraphy to confirm the diagnosis. The scintigraphy is done on the same day, the result of which corroborates the suspicion of PE. Once the diagnosis is established, factual knowledge bases propose the appropriate treatment based on heparinotherapy and platelets transfusion.

CONCLUSIONS

Real time systems providing intelligent monitoring are now necessary to meet the increasing demand for more acute and intensive care required by patients with complex disorders. In hemato-oncology departments, patients subjected to chemotherapeutic protocols present difficult monitoring problems for clinicians. Faced with a dramatically increasing number of variables, under time pressure in a rapidly changing environment, and risking potentially dangerous deteriorations of critically ill patients, clinicians have thus difficulties in establishing a clear picture of the world state to clarify their goals and assumptions. This problem motivated our research to design an intelligent control support system expected to help health professionals in the collection, storage, interpretation, and display of physiological data: SEPIA is a system which highlights relevant clinical information and therefore assists physicians in making an assessment of monitored data, and proposes adapted diagnostic and monitoring prescriptions as well as accurate therapy recommendations, all integrated into protocol-derived prescriptions in a patient specific care plan.

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